Notice of Allowability	Application No.	Applicant(s)	
	10/593,103	MASHIMA, YUKIHIKO	
	Examiner	Art Unit	
	AMANDA SHAW	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *the papers filed September 20, 2011*.

2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

3. ☒ The allowed claim(s) is/are *2,4,13,36,37 and 40-42*.

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☐ All b) ☐ Some* c) ☐ None of the:
      1. ☐ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
      3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.

6. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
   (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

7. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☒ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3. ☒ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date 8/13/2008
4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
5. ☐ Notice of Informal Patent Application
6. ☒ Interview Summary (PTO-413), Paper No./Mail Date *12/29/2011* .
7. ☒ Examiner's Amendment/Comment
8. ☒ Examiner's Statement of Reasons for Allowance
9. ☐ Other _____.

/Amanda Shaw/
Primary Examiner 1634

EXAMINER'S AMENDMENT

1. This action is in response to the papers filed September 20, 2011.

Claims 1-2, 4, 11-37, and 40-42 are currently pending.

Claims 2, 4, 13, and 40-42 are allowable. The restriction requirement between the different SNPs, as set forth in the Office action mailed on March 24, 2009, has been reconsidered in view of the allowability of claims to the elected invention pursuant to MPEP § 821.04(a). **The restriction requirement is hereby withdrawn as to any claim that requires all the limitations of an allowable claim.** Claims 36 and 37, directed to detecting additional SNPs are no longer withdrawn from consideration because the claim(s) requires all the limitations of an allowable claim. However, claims 1 and 14-28, directed to nucleic acids and compositions comprising nucleic acids; claim 11-12, directed to methods of diagnosing Leber's disease; claims 29-30, directed to methods for treating glaucoma; and claims 31-35, directed to methods for predicting the response of a subject to treatment with a drug remain withdrawn from consideration because they do not require all the limitations of an allowable claim.

In view of the above noted withdrawal of the restriction requirement, applicant is advised that if any claim presented in a continuation or divisional application is anticipated by, or includes all the limitations of, a claim that is allowable in the present application, such claim may be subject to provisional statutory and/or nonstatutory double patenting rejections over the claims of the instant application.

Once a restriction requirement is withdrawn, the provisions of 35 U.S.C. 121 are no longer applicable. See *In re Ziegler*, 443 F.2d 1211, 1215, 170 USPQ 129, 131-32 (CCPA 1971). See also MPEP § 804.01.

Information Disclosure Statement

2. The information disclosure statement (IDS) submitted on August 13, 2008 has been reconsidered by the Examiner. It is noted for the record that some of the references listed on page 4 have been crossed off. The references that have been crossed off have been considered by the Examiner however they will not be printed on the patent because they do not comply with the requirements of 37 CFR 1.98 which requires a date for each publication.

3. An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in a telephone interview with Alan Townsley on December 29, 2011.

4. The claims have been amended as follows:

1. (canceled).

2. (currently amended): A method for diagnosing or predicting susceptibility to open angle glaucoma in a human subject, comprising the steps of: i) obtaining a biological sample from the subject, ii) analyzing said sample to determine the presence or absence of a polymorphism in the noelin 2 gene that results in an arginine to glutamine change at amino acid position 144 of the noelin 2 protein; iii) analyzing said sample to determine the presence or absence of a polymorphism in the myocilin gene that results in a phenylalanine to leucine change at amino acid position 369 of the myocilin protein; and iv) making a diagnosis that said subject has, or is susceptible to, open angle glaucoma when said subject has at least one polymorphism selected from the group consisting of a polymorphism that results in a glutamine at amino acid position 144 of the noelin 2 protein and a polymorphism that results in a leucine at amino acid position 369 of the Myocilin protein.

3. (canceled).

4. (previously presented): The method of Claim 2, wherein said method further comprises analyzing said sample for the presence of at least one other genetic polymorphism associated with open angle glaucoma.

5-12. (canceled).

13. (currently amended): The method of Claim 2, wherein the analyzing comprises at least one technique selected from the group consisting of polymerase chain reaction (PCR), restriction fragment length polymorphism (PCR-RFLP) analysis, polymerase chain reaction followed by single strand conformation polymorphism (PCR-SSCP) analysis, ASO hybridization analysis, direct sequencing analysis, ARMS analysis, DGGE analysis, RNseA cleaving analysis, chemical restriction analysis, DPL analysis, TAQMAN® PCR analysis, INVADER® assay, MALDI-TOF/MS analysis, TDI analysis, single nucleotide extension assay, WAVE assay and a molecular fluorescent detection assay.

14-35. (canceled).

36. (currently amended): The method according to Claim 2, further comprising analyzing at least one genetic polymorphism selected from the group consisting of:
(1) AAG to AAT substitution at codon 198 of the endothelin-1 gene (Lys198Asn);
(2) - 1370T>G polymorphism of the endothelin-1 gene promoter region;
(3) A138 insertion/deletion(A 138I/D) polymorphism in exon 1 of the endothelin-1 gene;
(4) +70C>G polymorphism in 3' non-coding region of the endothelin receptor A gene; (5) +1222C>T polymorphism of the endothelin receptor A gene;
(6) CAC to CAT substitution at codon 323 in exon 6 of the endothelin receptor A gene

(His323His);

(7) -231A>G polymorphism of the endothelin receptor A gene promoter region;

(8) CTG to CTA substitution at codon 277 in exon 4 of the endothelin receptor B gene;

(9) 9099C>A polymorphism of the mitochondrial gene;

(10) 9101T>G polymorphism of the mitochondrial gene;

(11) 9101T>C polymorphism of the mitochondrial gene;

(12) 9804G>A polymorphism of the mitochondrial gene;

(13) 11778G>A polymorphism of the mitochondrial gene;

(14) -713T>G polymorphism of the angiotensin II type 1 receptor gene promoter region;

(15) 3123C>A polymorphism of the angiotensin II type 2 receptor gene;

(16) CAA to CGA substitution at codon 192 of the paraoxonase 1 gene (Gln192Arg);

(17) TTG to ATG substitution at codon 55 of the paraoxonase 1 gene (Leu55Met);

(18) GGA to CGA substitution at codon 389 of the β1 adrenergic receptor gene (Gly389Arg);

(19) 1402C>T polymorphism of the E-selectin gene;

(20) the combination of polymorphisms of -857C>T of the tumor necrosis factor a gene promoter region and 412G>A of the optineurin gene;

(21) the combination of polymorphisms of -863C>A of the tumor necrosis factor a gene promoter region and 603T>A of the optineurin gene;

(22) CGC to CCC substitution at codon 72 of the TP53 gene (Arg72Pro);

(23) TAC to CAC substitution at codon 113 of the microsomal epoxide hydrasel gene (Tyr113His);

(24) -110A>C polymorphism of the heatshock protein 70-1 gene promoter region;

(25) -338C>A polymorphism of the endothelin converting enzyme gene promoter region;

(26) -670A>G polymorphism of the CD95 gene promoter region;

(27) AAG to AAA substitution at codon 119 of the microsomal epoxide hydrase 1 gene(Lys 119Lys);

(28) GGA to AGA substitution at codon 16 of the β2 adrenergic receptor gene (Gly16Arg); and

(29) CAA to GAA substitution at codon 27 of the β2 adrenergic receptor gene (Gln27Glu).

37. (currently amended): The method according to Claim 2, further comprising analyzing genetic polymorphisms selected from the group consisting of: the combination of polymorphisms of -857C>T of the tumor necrosis factor α gene promoter region and 412G>A of the optineurin gene; and the combination of polymorphisms of -863C>A of the tumor necrosis factor α gene promoter region and 603T>A of the optineurin gene.

38-39. (canceled).

40. (previously presented): The method according to Claim 2, wherein said open angle glaucoma is primary open angle glaucoma or normal tension glaucoma.

41. (previously presented): The method according to Claim 2, wherein said open angle glaucoma is primary open angle glaucoma.

42. (previously presented): The method according to Claim 2, wherein said open angle glaucoma is normal tension glaucoma.

5. The following is an examiner's statement of reasons for allowance:

The rejection made under 35 USC 112 2nd paragraph in section 4 of the Office Action of April 20, 2011 is withdrawn in view of amendments made to the claims.

The rejection made under 35 USC 112 1st paragraph (enablement) in section 5 of the Office Action of April 20, 2011 is withdrawn in view of the Applicants arguments and the prior art of Fingert et al. (Human Molecular Genetics 1999 Vol 9 No 5 pages 899-905). The reference teaches that 1703 open angle glaucoma patients were screened for mutations in the myocilin gene. Overall, 61 different myocilin sequence variations were identified. Of the 61 variations, 21 were judged to be probable disease causing mutations (abstract). The following criteria were used to determine which mutations were probable disease causing mutations: (i) altered the predicted myocilin amino acid sequence; (ii) were present in one or more glaucoma subjects; (iii) were present in <1% of the general population; and (iv) were absent from the normal controls (page 900). In the instant case the claimed polymorphism in the Myocilin gene meets each of the criteria: it alters the myocilin amino acid sequence since it results in a phenylalanine to leucine change at amino acid position 369 of the Myocilin protein; it

was present in 1 out of 171 primary open angle glaucoma patients; it was present in less than 1% of the general population (i.e., 1/271); and it was absent from 100 normal controls. Thus based on the teachings in the prior art regarding polymorphisms in the myocilin gene, the claimed polymorphism in the Myocilin gene would be considered by one of ordinary skill in the art to be a probable disease causing mutation. Further it is noted that because the noelin-2 gene is structurally and functionally related to myocilin, the same criteria has been used to determine whether the claimed mutation is a disease causing mutation. In the instant case the claimed polymorphism in the Noelin-2 gene meets each of the criteria: it alters the Noelin-2 amino acid sequence since it results in an arginine to glutamine change at amino acid position 144 of the Noelin-2 protein; it was present in 1 out of 276 primary open angle glaucoma patients and 1 out of 340 normal tension glaucoma patients; it was present in less than 1% of the general population (i.e., 2/916); and it was absent from 300 normal controls. Thus the claimed polymorphism in the Noelin-2 gene would be considered by one of ordinary skill in the art to be a probable disease causing mutation. For this reason the enablement rejection is withdrawn.

6. Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to AMANDA SHAW whose telephone number is (571)272-8668. The examiner can normally be reached on Mon-Fri 9:00 TO 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on (571) 272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Amanda Shaw/
Primary Examiner 1634